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Synthesis of Spirohydantoins and Schiff Bases of Indenoquinoxalinones and Indenopyridopyrazinones

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The main structure of many compounds containing spirohydantoin and Schiff bases of indenoquinoxalines and indenopyridopyrazinones expose valuable pharmacological properties. Herein, an effective synthesis and stereochemistry of indenoquinoxalinones (**2a, 2b+bi~2d+di**) and indenopyridopyrazinones (**2e+ei~g+gi**) *via* the reaction of ninhydrin with desirable diamines is reported. We synthesized the corresponding spirohydantoins (**3a, 3b~d** and **3bi~di**) from synthesized indeno[1,2-*b*]quinoxalinones and indeno[1,2-*b*]pyrido[3,2-*e*]pyrazinones with the standard Bucherer-Bergs conditions (KCN, ammonium carbonate, acetonitrile, refluxing, without $NaHSO_3$). And also synthesized the azomethine analogs (**4~8+8i**) of tetracyclic indeno[1,2-*b*]quinoxalinones as a Schiff base.

Keywords: Spirohydantoin, Indenoquinoxalinones, Indenopyridopyrazinones, Ninhydrin, Diamine.

INTRODUCTION

Much attention during the past few years has been focused to a large range of nitrogen-containing heterocyclics and heterocyclic indenoquinoxalines because of their pharmacological properties and clinical applications [1-7]. Indenoquinoxalines as a significant group of aza-polycyclics are important classes of *N*-heterocycles since are useful intermediates for spiroindeno synthesis. The main structure of many spiro compounds containing spiroindenoquinoxalines expose valuable pharmacological properties such as anticancer, antitumor agents and antibacterial treatments, antimicrobial action of particular interest [8,9]. Especially spiro-*N*-heterocycles are also of noticeable interest because of the presence of a spirocarbon supplies a fortifying of the structural frame and together with a varity of hydantoins and spirohydantoins are the main significant core of many pharmacological agents [10,11].

Existing spirohydantoin and indenoquinoxaline moieties in structure of one spiro compound can be attractive to organic and bioorganic scientists due to the integration of more than one *N*-heterocyclic scaffold in structure of molecule causes interesting bioorganic and biological properties [12-18]. As away of our efforts to discover and develop novel studies on a group of spiroindenoquinoxalines with bicyclic group spiro-attachted to hydantoin ring, herein the synthesis, stereochemistry and biological evaluation of new spiroindenoquinoxalines derivatives as potential pharmacological agents. Pharmacologically hydantoin and spirohydantoin derivatives possess a range of biochemical and pharmacological properties and subsequently are used to treat many human diseases as anticonvulsants in the treatment of seizure disorders, a muscle relaxant to treat neuroleptic malignant syndrome, malignant hyperthermia, ecstasy intoxication and spasticity [18,19]. But, there are only few studies concentrating on their potential as cancer therapeutic agents. In present work, develop a special and resourceful process for the combinatorial synthesis of a spiro-substituted indenoquinoxalines library for biological screening.

EXPERIMENTAL

Except where explicitly stated, all chemicals were purchased from Aldrich, Fisher and TCI, and used as received. Melting points were established using an electrothermal capillary melting point equipment and are uncorrected. ^1H & ^{13}C NMR spectra were analyzed with Bruker AC 2000 (200 MHz) and Varian Gemini (200 or 300 MHz) spectrometers. Mass spectra were calculated with HP 5890 GC/Mass (70 eV, EI).

Indeno[1,2-*b*]pyrido[3,2-*e*]pyrazine-6-one: Ninhydrin (0.06 mol) and phenylenediamine (0.06 mol) were dissolved in MeOH (15 mL). The reaction mixture was allowed to mix at room temperature and observed by TLC to the point of completion. After mixing for 24 h, the reaction was poured into 15 mL of ice-water and the solid material was gathered. This material was then dissolved in CH_2Cl_2. The remaining residual water in the organic layer was separated from and dried over $MgSO_4$. Products were purified by column chromatography to afford the following compounds **2a**-**2gi**.

11*H*-Indeno[1,2-*b*]quinoxalin-11-one (2a): Yield: 93.2%; m.p.: 151-153 ºC; R_f: 0.82 (TLC eluent; ethyl acetate:*n*-hexane = 1:1, v/v). Mass (70 eV), *m/z* (rel. int. %): 234.07 (1.2), 233.07 (16.2), 232.06 (100); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.22 (d, 1H), 8.08 (dd, 2H), 7.91 (d, 1H), 7.76 (dd, 3H), 7.59 (d, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.41, 156.58, 149.94, 142.26, 141.96, 141.08, 137.06, 136.76, 132.88, 132.55, 131.07, 130.47, 129.49, 124.33, 122.39. Elemental analysis calcd. (found) %: C, 77.58 (77.58); H, 3.47 (3.47); N, 12.06 (12.06); O, 6.89 (6.89).

7-Methyl-11*H*-indeno[1,2-*b*]quinoxalin-11-one (2b): Yield: 90.4%; m.p.: 113-115 ºC; R_f: 0.79 (TLC eluent; ethyl acetate:*n*-hexane = 1:1, v/v). Mass (70 eV), *m/z* (rel. int. %): 248.09 (1.4), 247.08 (17.3), 246.08 (100); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.05 (d, 2H), 7.94 (d, 1H), 7.86 (m, 2H), 7.70 (dd, 2H), 2.58 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.39, 156.59, 148.87, 143.25, 142.22, 140.27, 136.83, 132.64, 132.34, 130.52, 129.87, 126.90, 126.45, 124.14, 122.15, 21.41. Elemental analysis calcd. (found) %: C, 78.02 (78.03); H, 4.05 (4.09); N, 11.39 (11.38); O, 6.51 (6.50).

8-Methyl-11*H*-indeno[1,2-*b*]quinoxalin-11-one (2bi): Yield: 90.4%; m.p.: 106-107 ºC; R_f: 0.79 (TLC eluent; ethyl acetate:*n*-hexane = 1:1, v/v). Mass (70 eV), *m/z* (rel. int. %): 248.09 (1.4), 247.08 (17.3), 246.08 (100); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.05 (d, 2H), 7.94 (d, 1H), 7.86 (m, 2H), 7.70 (dd, 2H), 2.58 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.42, 156.60, 143.24, 141.92, 140.95, 140.73, 136.90, 136.84, 134.42, 129.87, 128.20, 124.19, 124.22, 122.15, 21.40. Elemental analysis calcd. (found) %: C, 78.02 (78.03); H, 4.05 (4.09); N, 11.39 (11.38); O, 6.51 (6.50).

7-Chloro-11*H*-indeno[1,2-*b*]quinoxalin-11-one (2c): Yield: 90.4%; m.p.: 149-150 ºC; R_f: 0.78 (TLC eluent; ethyl acetate:*n*-hexane = 1:1, v/v). Mass (70 eV), *m/z* (rel. int. %): 267.03 (16.2), 268.02 (32), 266.02 (100); ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 7.57 (m, 3H), 7.36 (m, 4H). Elemental analysis calcd. (found) %: C, 67.56 (67.57); H, 2.65 (2.69); Cl, 13.29 (13.30); N, 10.50 (10.52); O, 6.00 (6.01).

8-Chloro-11*H*-indeno[1,2-*b*]quinoxalin-11-one (2ci): Yield: 90.4%; m.p.: 391-394 ºC; R_f: 0.78 (TLC eluent; ethyl acetate:*n*-hexane = 1:1, v/v). Mass (70 eV), *m/z* (rel. int. %): 267.03 (16.2), 268.02 (32), 266.02 (100); ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 7.57 (m, 3H), 7.36 (m, 4H) Elemental analysis calcd. (found) %: C, 67.56 (67.57); H, 2.65 (2.69); Cl, 13.29 (13.30); N, 10.50 (10.52); O, 6.00 (6.01).

7-Benzoyl-11*H*-indeno[1,2-*b*]quinoxalin-11-one (2d): Yield: 95.7%; m.p.: 88-90 ºC; R_f: 0.81 (TLC eluent; ethyl acetate:*n*-hexane = 1:1, v/v). Mass (70 eV), *m/z* (rel. int. %): 338.10 (2.7), 337.09 (23.8), 331.09 (100). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.60 (d, 1H), 8.33 (d, 1H), 8.26 (m, 1H), 8.17 (dd, 2H), 7.96 (m, 1H), 7.88 (m, 2H), 7.83 (m, 1H), 7.68 (m, 1H), 7.54 (m, 1H), 7.26 (m, 1H); ^{13}C-NMR (DMSO-d_6, 100 MHz): δ 195.01, 189.21, 159.46, 151.58, 144.52, 141.45, 141.11, 138.31, 137.55, 136.88, 133.83, 133.68, 133.26, 132.20, 130.28, 129.23, 124.81, 123.19. Elemental analysis calcd. (found) %: C, 78.55 (78.54); H, 3.66 (3.69); N, 8.33 (8.31); O, 9.51 (9.51).

8-Benzoyl-11*H*-indeno[1,2-*b*]quinoxalin-11-one (2di): Yield: 95.7%; m.p.: 96-97 ºC; R_f: 0.81 (TLC eluent; *n*-hexane :ethyl acetate = 1:1, v/v). Mass (70 eV), *m/z* (rel. int. %): 338.10 (2.7), 337.09 (23.8), 336.09 (100); ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 8.61 (d, 1H), 8.33 (d, 1H), 8.26 (m, 1H), 8.17 (dd, 2H), 7.96 (m, 1H), 7.88 (m, 2H), 7.83 (m, 1H), 7.66 (m, 1H), 7.54 (m, 1H), 7.26 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 195.01, 189.22, 158.48, 151.59, 144.52, 141.45, 141.11, 138.31, 137.55, 136.88, 133.83, 133.68, 133.26, 132.20, 130.28, 129.22, 124.81, 123.19. Elemental analysis calcd. (found) %: C, 78.56 (78.54); H, 3.66 (3.69); N, 8.33 (8.31); O, 9.51 (9.51).

6*H*-Indeno[1,2-*b*]pyrido[3,2-*e*]pyrazin-6-one (2e): Yield: 97.7%; m.p.: 96-97 ºC; R_f: 0.81 (TLC eluent; ethyl acetate:*n*-hexane = 1:1, v/v). Mass (70 eV), *m/z* (rel. int. %): 234.06 (1.1), 234.06 (15.1), 233.06 (100); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.15 (d, 1H), 8.62 (d, 1H), 8.17 (m, 1H), 7.91 (dd, 2H), 7.76 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 189.91, 159.97, 155.68, 151.48, 151.33, 141.11, 140.24, 137.57, 133.85, 126.11, 124.77, 123.36. Elemental analysis calcd. (found) %: C, 72.10 (72.14); H, 3.03 (3.01); N, 18.02 (18.02); O, 6.86 (6.87).

10*H*-Indeno[1,2-*b*]pyrido[2,3-*e*]pyrazin-10-one (2ei): Yield: 97.7%; m.p.: 96-97 ºC; R_f: 0.81 (TLC eluent; ethyl acetate:*n*-hexane = 1:1, v/v). Mass (70 eV), *m/z* (rel. int. %): 236.07 (1.1), 236.08 (15.1), 235.07 (100); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.15 (d, 1H), 8.62 (d, 1H), 8.17 (m, 1H), 7.92 (dd, 2H), 7.76 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 189.91, 159.97, 155.68, 151.48, 151.33, 141.11, 140.24, 137.57, 133.85, 126.11, 124.77, 123.36. Elemental analysis calcd. (found) %: C, 72.10 (72.14); H, 3.03 (3.01); N, 18.02 (18.02); O, 6.86 (6.87).

6*H*-Indeno[1,2-*b*]pyrido[4,3-*e*]pyrazin-6-one (2f): Yield: 91.35%; m.p.: 246-247ºC; R_f: 0.77 (TLC eluent; ethyl acetate:*n*-hexane = 1:1, v/v). Mass (70 eV), *m/z* (rel. Int. %): 234.06 (1.1), 234.06 (15.1), 233.06 (100); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.60 (d, 1H), 8.33 (d, 2H), 8.26 (m, 1H), 8.17 (dd, 2H), 7.88 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 189.33, 157.80, 150.74, 143.05, 141.03, 140.98, 137.46, 133.61, 132.98, 131.18, 128.18, 124.74, 122.98. Elemental analysis calcd. (found) %: C, 72.10 (72.10); H, 3.03 (3.06); N, 18.02 (18.04); O, 6.86 (6.87).

10*H*-Indeno[1,2-*b*]pyrido[3,4-*e*]pyrazin-10-one (2fi): Yield: 91.35%; m.p.: 246-247 ºC; R_f: 0.77 (TLC eluent; ethyl acetate:*n*-hexane = 1:1, v/v). Mass (70 eV), *m/z* (rel. Int. %): 234.06 (1.1), 234.06 (15.1), 233.06 (100); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.60 (d, 1H), 8.33 (d, 2H), 8.26 (m, 1H), 8.17 (dd, 2H), 7.88 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 189.33, 157.80, 150.74, 143.05, 141.03, 140.98, 137.46, 133.61, 132.98, 131.18, 128.18, 124.74, 122.98. Elemental analysis calcd. (found) %: C, 72.10 (72.10); H, 3.03 (3.06); N, 18.02 (18.04); O, 6.86 (6.87).

3-Bromo-10*H*-indeno[1,2-*b*]pyrido[2,3-*e*]pyrazin-10-one (2g): Yield: 96.0%; m.p.: 140-142 ºC; R_f: 0.25 (TLC eluent; ethyl acetate:*n*-hexane = 1:1, v/v). Mass (70 eV), *m/z* (rel. Int. %): 311.97 (15.1), 312.97 (97.3), 310.97 (100); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.22 (d, 1H), 8.98 (d, 1H), 8.17 (m, 1H), 7.94 (dd, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 189.01, 158.35, 156.08, 154.49, 153.53, 150.18, 141.53, 140.17, 138.96, 137.66, 133.96, 124.91, 123.16, 120.79. Elemental analysis calcd. (found) %: C, 53.87 (53.88); H, 1.94 (1.94); Br, 25.60 (25.61); N, 13.46 (13.46); O, 5.13 (5.13).

3-Bromo-6*H*-indeno[1,2-*b*]pyrido[3,2-*e*]pyrazin-6-one (2gi): Yield: 96.0%; m.p.: 140-142ºC; R_f: 0.25 (TLC eluent; ethyl acetate:*n*-hexane = 1:1, v/v). Mass (70 eV), *m/z* (rel. Int. %): 311.97 (15.1), 312.97 (97.3), 310.97 (100); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.22 (d, 1H), 8.98 (d, 1H), 8.17 (m, 1H), 7.94 (dd, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 182.91, 158.35, 156.08, 154.49, 153.53, 150.18, 141.53, 140.17, 138.96, 137.66, 133.96, 124.91, 123.15, 120.79. Elemental analysis calcd. (found) %: C, 53.87 (53.88); H, 1.94 (1.95); Br, 25.60 (25.61); N, 13.46 (13.46); O, 5.13 (5.13).

Spirohydantoins : Indeno[1,2-*b*]quinoxalin-11-one (0.03 mol), KCN (0.045 mol) and ammonium carbonate (0.06 mol) were dissolved in acetonitrile (75 mL). The reaction mixture was heated under stirring to 80 ºC for 72 h. After cooling to room temperature, the mixture was water down with 35 mL of water and filtered. The filtrate was acidified with diluted HCl to pH 7 and permited to mix at room temperature for 30 min. The precipitated solids were gathered by filteration, air dried and recrystallized from CH_2Cl_2-CH_3OH to give **3a**-**3di**.

Spirohydantoin 3a: Yield: 50.7%; R_f: 0.81 (TLC eluent ; *n*-hexane:ethyl acetate = 1:1, v/v); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.708 (d, 1H), 8.196 (d, 1H), 7.907 (m, 1H), 7.796 (dd, 2H), 7.719 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 172.860, 158.247, 153.622, 142.406, 140.827, 137.245, 132.991, 131.213, 130.316, 129.346, 129.146, 124.902, 122.479, 70.064.

Spirohydantoin 3b: Yield: 43.3% ; R_f: 0.81 (TLC eluent ; *n*-hexane:ethyl acetate = 1:1, v/v); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.708 (d, 1H), 8.196 (d, 1H), 7.907 (m, 1H), 7.796 (dd, 2H), 7.719 (m, 1H), 2.674 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 172.860, 158.247, 153.622, 142.406, 140.827, 137.245, 132.991, 131.213, 130.316, 129.346, 129.146, 124.902, 122.479, 70.064, 23.233.

Spirohydantoin 3c: Yield: 60.2%; R_f : 0.35 (TLC eluent ; *n*-hexane:ethyl acetate = 2:1, v/v); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.742 (d, 1H), 8.165 (d, 1H), 7.696 (m, 1H), 6.912 (dd, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 167.518, 154.614, 142.807, 139.496, 135.295, 133.304, 131.040, 127.903, 124.623, 122.627, 120.259, 109.644, 108.484, 67.414.

Spirohydantoin 3d: Yield: 46.3%; R_f : 0.35 (TLC eluent ; *n*-hexane:ethyl acetate = 2:1, v/v); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.504 (s, 1H), 8.364 (d, 1H), 8.238 (m, 2H), 7.881 (m, 3H), 7.746 (m, 3H), 7.625 (m, 3H), 4.796 (s, 1H).

Schiff bases: Indeno[1,2-*b*]quinoxalin-11-one (0.03 mol) and 4-fluoroaniline (0.03 mol) were dissolved in CH_3Cl (30 mL). The reaction mixture was allowed to stir at 40 ºC. After stirring for 48 h, cool to room temperature, the mixture was poured with 30 mL of water and filtered. The filtrate was permited to mix at room temperature for 30 min. The precipitated solids were gathered by filteration, air dried and recrystallized from CH_2Cl_2-MeOH to give products, which were purified by column chromatography to afford the corresponding compounds **4**-**8i**.

Schiff base 4: Yield: 75.2% ; R_f: 0.72 (TLC eluent; *n*-hexane:ethyl acetate = 2:1, v/v); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.324 (d, 1H), 8.202 (d, 1H), 7.773 (m, 1H), 7.605 (dd, 2H), 7.273 (m, 1H), 7.191 (d, 2H), 7.089 (dd, 2H), 6.922 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 161.571, 159.150, 154.518, 151.573, 147.118, 147.089, 143.395, 142.595, 140.275, 133.547, 131.143, 131.265, 131.046, 129.907, 129.470, 126.800, 122.870, 119.584, 116.497, 116.272.

Schiff base 5: Yield: 78.5 %; R_f: 0.69 (TLC eluent; *n*-hexane: ethyl acetate = 2:1, v/v); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.078 (d, 2H), 8.057 (m, 6H), 7.705 (m, 4H), 2.587 (s, 3H), 1.987 (s, 3H).

Schiff base 6: Yield: 76.5% ; R_f: 0.72 (TLC eluent; *n*-hexane:ethyl acetate = 2:1, v/v); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.196 (d, 1H), 8.993 (d, 1H), 8.987 (m, 6H), 8.093 (dd, 1H), 7.933 (m, 2H), 7.785 (m, 1H), 7.777 (m, 1H), 2.449 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 161.526, 159.707, 157.435, 155.843, 154.882, 153.573, 151.536, 142.885, 142.285, 141.986, 141.523, 140.317, 139.046, 135.436, 135.318, 126.264, 124.855, 124.509, 124.301, 122.145.

Schiff base 7: Yield: 75.2%; R_f: 0.72 (TLC eluent; *n*-hexane: ethyl acetate = 2:1, v/v); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.302 (d, 3H), 7.774 (m, 2H), 7.418 (dd, 2H), 7.368 (m, 2H), 7.282 (m, 1H), 7.095 (m, 1H).

Schiff base 8: Yield: 60.2% ; R_f: 0.72 (TLC eluent; *n*-hexane :ethyl acetate = 2 : 1, v/v); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.223 (d, 1H), 8.088 (d, 1H), 7.765 (m, 1H), 7.597 (dd, 3H), 7.260 (m, 4H), 1.679 (s, 3H).

RESULTS AND DISCUSSION

We report here in an effective synthesis and stereochemistry of indenoquinoxalinones and indenopyridopyrazinones *via* the reaction of ninhydrin with a variety of reagents as phenylenediamines, diaminopyridines, and diaminobenzophenone. A multi-component reaction between indenoquinoxalinones, potassium cyanide and ammonium carbonate, which result in the formation of spirohydantoins derived indenoquinoxalinones. Indenoquinoxalinones reacted quantitatively with highly funtionalized amines by refluxing to give Schiff bases derived indenoquinoxalinones with high yield. First of all the adjacent access of a hydroxyl group of ninhydrin to the presence of carbonyl groups makes this extremely reactive compound an attractive starting point for cascade reactions with diamino starting materials. The reaction of ninhydrin with *o*-phenylenediamine in MeOH is fully regiospecific and afforded the corresponding indeno[1,2-*b*]quinoxalin-11-one in 93.2% yield without the aid of any catalysts. A reasonable reaction mechanism is addition to C=O and substitution of two OH resulting from elimination of two water. IR spectrum of indeno[1,2-*b*]quinoxalin-11-one confirmed the existence of –C=N and C=O absorption bands at 1605 and 1728 cm^{-1}. The ^{1}H NMR spectrum revealed the ArH at δ 7.25-8.20 ppm. The mass spectrum indicated a molecular ion peak (M+) at *m/z* = 232.34 according to the molecular weight

of the molecular formula $C_{15}H_8N_2O$ = 232.23. As illustrated, indenoquinoxalinones and indenopyridopyrazinones are significant classes of nitrogen containing heterocycles and they consist useful intermediates in organic synthesis. In view of the biochemical and biological importance of indenoquinoxalinones and indenopyridopyrazinones, we report synthesis of indeno[1,2-*b*]quinoxalinones (**2a**, **2b+bi~2d+di**) and indeno-[1,2-*b*]pyrido[3,2-*e*]pyrazin-6-ones (**2e+ei~g+gi**) from the reactions of ninhydrin with various phenylenediamines (*o*-phenylenediamine (**1a**), 3,4-diaminotoluene (**1b**), 4-chloro-1,2-phenylenediamine (**1c**), 3,4-diaminobenzophenone (**1d**), 2,3-diaminopyridine (**1e**), 3,4-diaminopyridine (**1f**), 2,3-diamino-5-bromopyridine (**1g**), indeno[1,2-*b*]quinoxalin-11-one (**2a**), 7-methyl-11*H*-indeno[1,2-*b*]quinoxalin-11-one (**2b**), 8-methyl-11*H*-indeno[1,2-*b*]quinoxalin-11-one (**2bi**), 7-chloro-11*H*-indeno[1,2-*b*]quinoxalin-11-one (**2c**), 8-chloro-11*H*-indeno-[1,2-*b*]quinoxalin-11-one (**2ci**), 7-benzoyl-11*H*-indeno[1,2-*b*]-quinoxalin-11-one (**2d**), 8-benzoyl-11*H*-indeno[1,2-*b*]quinoxalin-11-one (**2di**), 6*H*-indeno[1,2-*b*]pyrido[3,2-*e*]pyrazin-6-one (**2e**), 10*H*-indeno[1,2-*b*]pyrido[2,3-*e*]pyrazin-10-one (**2ei**), 6*H*-indeno[1,2-*b*]pyrido[4,3-*e*]pyrazin-6-one (**2f**), 10*H*-indeno-[1,2-*b*]pyrido[3,4-*e*]pyrazin-10-one (**2fi**), 3-bromo-10*H*-indeno-[1,2-*b*]pyrido[2,3-*e*]pyrazin-10-one (**2g**), 3-bromo-6*H*-indeno-[1,2-*b*]pyrido[3,2-*e*]pyrazin-6-one (**2gi**). From here, we have a lot of concern for the stereochemistry of synthesized 11*H*-indeno[1,2-*b*]quinoxalin-11-ones and indeno[1,2-*b*]pyrido-[3,2-*e*]pyrazin-6-ones. As illustrated in Table-1, 7-methyl-11*H*-indeno[1,2-*b*]quinoxalin-11-one (**2b**) and 8-methyl-11*H*-indeno-[1,2-*b*]quinoxalin-11-one (**2bi**) as a stereoisomer were obtained with 90.4% yield by the reaction of ninhydrin with 3,4-diaminotoluene. The ^{1}H NMR spectrum of **2b**-CH_3 and **2bi**-CH_3 showed band at δ 2.60 ppm and 2.62 ppm, respectively. We couldn't separate **2b** and **2bi** as a single product. Compounds **2c~g** and **2c′~g′** as structural isomers like **2b** and **2bi** to form spirohydantoins and imines were used without separation. Spirohydantoin derivatives possess a range of biochemical and pharmacological characteristic and subse-quently are used to treat many human diseases. Synthesis of spirohydantoin from synthesized indeno-[1,2-*b*]quinoxalinones and indeno[1,2-*b*]pyrido[3,2-*e*]pyrazinones of a series of substituted spirohydantoins are described herein. When indeno[1,2-*b*]quinoxalinones were subjected to the standard Bucherer-Bergs conditions (KCN, $(NH_4)_2CO_3$, acetonitrile, refluxing, without $NaHSO_3$), spirohydantoins were isolated with high yield. Initially, we prepared spiro[imidazolidine-4,11′-indeno[1,2-*b*]quinoxaline]-2,5-dione (**3a**) from indeno[1,2-*b*]-quinoxalin-11-one (**2a**) with high yield as shown in Table-2 and **Scheme-I**.

The chemical structure of compound **3a** synthesized from compound **2a** was constituted on the base of spectral data. The ^{1}H NMR spectrum of compound **3a** revealed peaks of eight hydrogens for two ArH at δ 7.7-8.7 ppm. The mass spectrum indicated a molecular ion peak(M+) at *m/z* = 303.15 (M^+ + 1), according to the molecular weight of the molecular formula $C_{17}H_{10}N_4O_2$ = 302.36. In a similar way, 7′-methylspiro[imidazolidine-4,11′-indeno[1,2-*b*]quinoxaline]-2,5-dione (**3b**) and 8′-methylspiro[imidazolidine-4,11′-indeno[1,2-*b*]quinoxaline]-2,5-dione (**3bi**) from compounds **2b** and **2bi**, 7′-chlorospiro-

TABLE-1
PHYSICAL DATA AND YIELDS OF INDENO QUINOXALINONES AND INDENO PYRIDOPYRAZINONES

Diamine	Product	Reaction time (h)	m.p. (°C)	Yield[a] (%)
1a	**2a**	12	151-153	93.2
1b	**2b+2bi**	12	156-160	90.4
1e	**2e+2ei**	12	131-132	97.7
1f	**2f+2fi**	24	160-162	91.3
1c	**2c+2ci**	12	126-129	90.4
1g	**2g+2gi**	12	154-155	96.0
1d	**2d+2di**	12	128-133	95.7

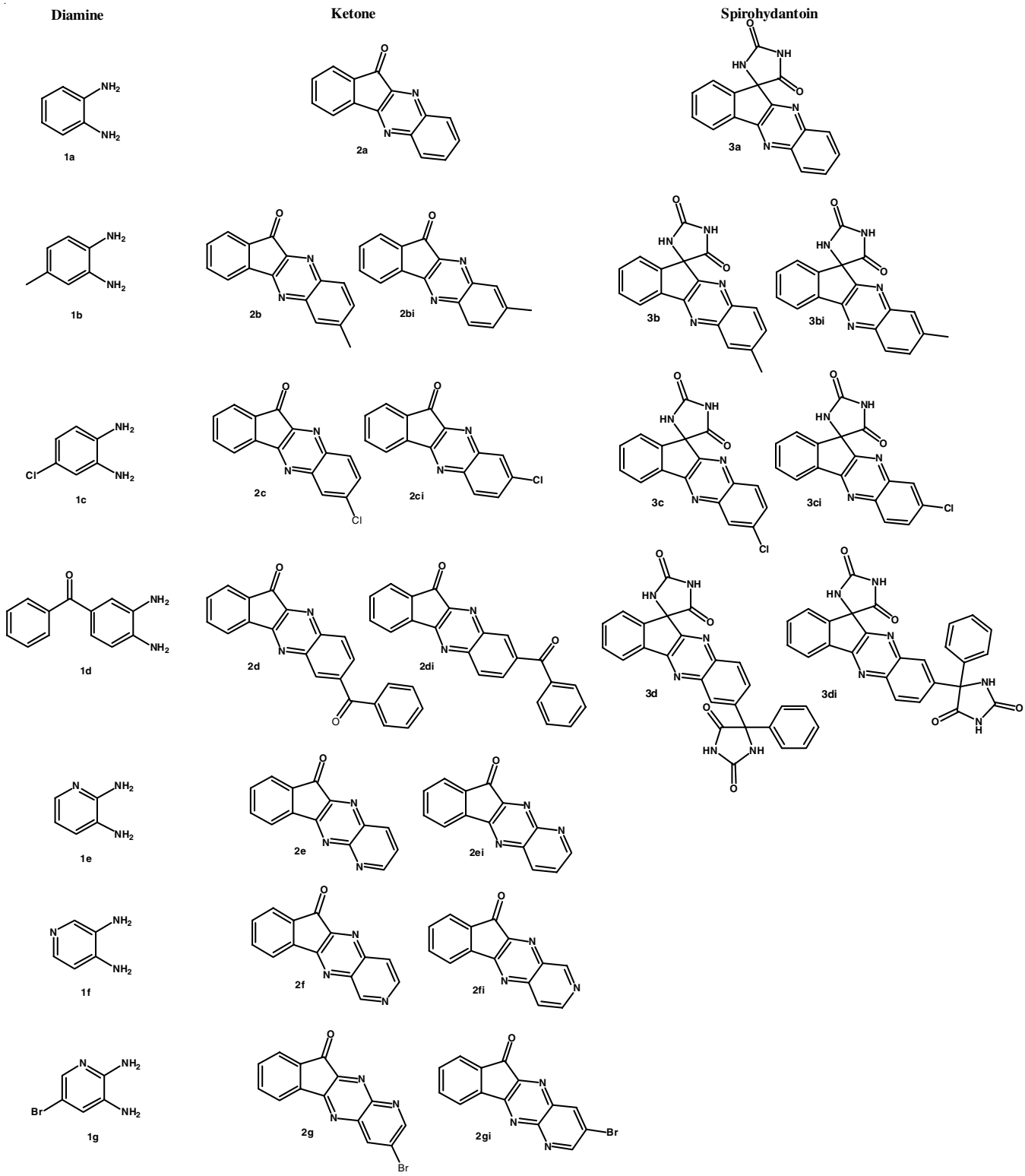
[a]All products were characterized using GC/MS and compared with authentic samples

TABLE-2
PHYSICAL DATA AND YIELDS OF SPIROHYDANTOIN DERIVATIVES

Starting material	Product	Reaction time (h)	m.p. (°C)	Yield[a] (%)
2a	**3a**	72	185-187	50.7
2b+2bi	**3b+3bi**	72	184-190	43.3
2c+2ci	**3c+3ci**	72	177-180	60.2
2d+2di	**3d+3di**	72	189-190	46.3

[a]All products were characterized using GC/MS and compared with authentic samples.

[imidazolidine-4,11′-indeno[1,2-*b*]quinoxaline]-2,5-dione (**3c**) and 8′-chlorospiro[imidazolidine-4,11′-indeno[1,2-*b*]-quinoxaline]-2,5-dione (**3ci**) from cmpounds **2c** and **2ci**, and 7′-(2,5-dioxo-4-phenylimidazolidin-4-yl)spiro[imidazolidine-4,9′-indeno[1,2-*b*]pyrazine]-2,5-dione (**3d**) and 8′-(2,5-dioxo-4-phenylimidazolidin-4-yl)spiro[imidazolidine-4,9′-indeno-[1,2-*b*]pyrazine]-2,5-dione (**3di**) from compounds **2d** and **2di** were synthesized with high yield. Like synthesized 11*H*-indeno-[1,2-*b*]quinoxalin-11-ones and indeno[1,2-*b*]pyrido[3,2-*e*]-pyrazin-6-ones, we couldn't isolate spiroisomers **3b~d** and **3bi~di** synthesized from **2b~d** and **2bi~di**. Separation of synthesized isomers as a single product was the most difficult problem. In continuation of our research for potential anticancer agents, the present Schiff base synthesis describes azomethine analogs of tetracyclic indeno[1,2-*b*]quinoxalinones. A mixture of indeno-[1,2-*b*]quinoxalin-11-one (**2a**) and 4-fluoroaniline in $CHCl_3$ and HCl was refluxed for 48 h. Progress of reaction was confirmed by TLC. The mixture was cooled and concentrated, then dissolved in water, neutralized by K_2CO_3 and extracted with CH_2Cl_2 thrice. The organic layer evaporated *in vacuo* and purified by column chromatography (*n*-hexane:ethyle acetate = 10:1, v/v). The residue was dried to give (*Z*)-*N*-(4-fluorophenyl)-11*H*-indeno[1,2-*b*]-quinoxalin-11-imine (**4**) as a yellow solid with 75.2% yield. The evidence of formation for (*Z*)-*N*-(4-fluorophenyl)-11*H*-indeno[1,2-*b*]quinoxalin-11-imine (**4**) using ^{1}H NMR spectrum revealed peaks of eleven hydrogens for three ArHs at δ 6.9~8.4 ppm. The mass spectrum showed a molecular ion peak (M+) at *m/z* = 326. 326.21 (M^+ + 1), corresponding to the molecular weight of the molecular formula $C_{17}H_{10}N_4O_2$ = 325.23. In a similar way, (*Z*)-*N*-(4-fluorophenethyl)-11*H*-indeno[1,2-*b*]-quinoxalin-11-imine (**5**), (*Z*)-*N*-(3-fluoro-4-methylphenyl)-11*H*-indeno[1,2-*b*]quinoxalin-11-imine (**6**), (*Z*)-*N*-(4-fluoro-



Scheme-I: Structure of indenoquinoxalines, indeno pyridopyrazinones and spirohydantoins

3-nitrophenyl)-11*H*-indeno[1,2-*b*]quinoxalin-11-imine (**7**), (*Z*)-*N*-(4-fluorophenyl)-7-methyl-11*H*-indeno[1,2-*b*]quinoxalin-11-imine (**8**) and (*Z*)-*N*-(4-fluorophenyl)-8-methyl-11*H*-indeno[1,2-*b*]quinoxalin-11-imine (**8i**) as Schiff bases from the corresponding amine (4-fluorophenethylamine, 3-fluoro-4-methylaniline, 4-fluoro-3-nitroaniline or 4-fluoroaniline) were synthesized with high yield (Table-3 and **Scheme-II**).

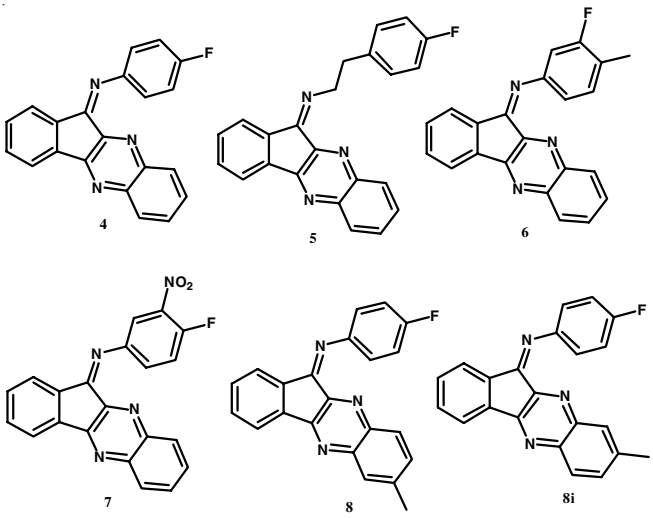
Conclusion

An effective synthesis and stereochemistry of indenoquinoxalinones and indenopyridopyrazinones *via* the reaction of ninhydrin with a variety of reagents as phenylenediamines, diaminopyridines and diaminobenzophenone are reported. A multi-component reaction between indenoquinoxalinones, KCN and $(NH_4)_2CO_3$, which contribute to the formation of spirohyd-

TABLE-3
PHYSICAL DATA AND YIELDS OF SCHIFF BASE DERIVATIVES (**4-8**)

Diamine	Product	Reaction time (h)	m.p. (°C)	Yield[a] (%)
2a	**4**	48	131-133	75.2
2a	**5**	48	138-130	78.5
2a	**6**	48	125-130	76.5
2a	**7**	48	129-130	75.2

[a]All products were characterized using GC/MS and compared with authentic samples.



Scheme-II: Structure of Schiff base derivatives

antoins derived indenoquinoxalinones. Indenoquinoxalinones reacted quantitatively with highly funtionalized amines by refluxing to give Schiff bases derived indenoquinoxalinones with high yield. Effectively indenoquinoxalinones, indenopyridopyrazinones, Schiff bases derived from indenoquinoxalinones, spirohydantoins formed from synthesized indeno[1,2-*b*]quinoxalinones and indeno[1,2-*b*]pyrido[3,2-*e*]pyrazinones are the most important bioactive materials *in vivo*. Continually synthesis of novel meterials and bioactive evaluations of synthesized all products will be executed.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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